



NTP
National Toxicology Program

Toxicology and Carcinogenesis Studies of Genistein in Sprague-Dawley Rats

TR 545



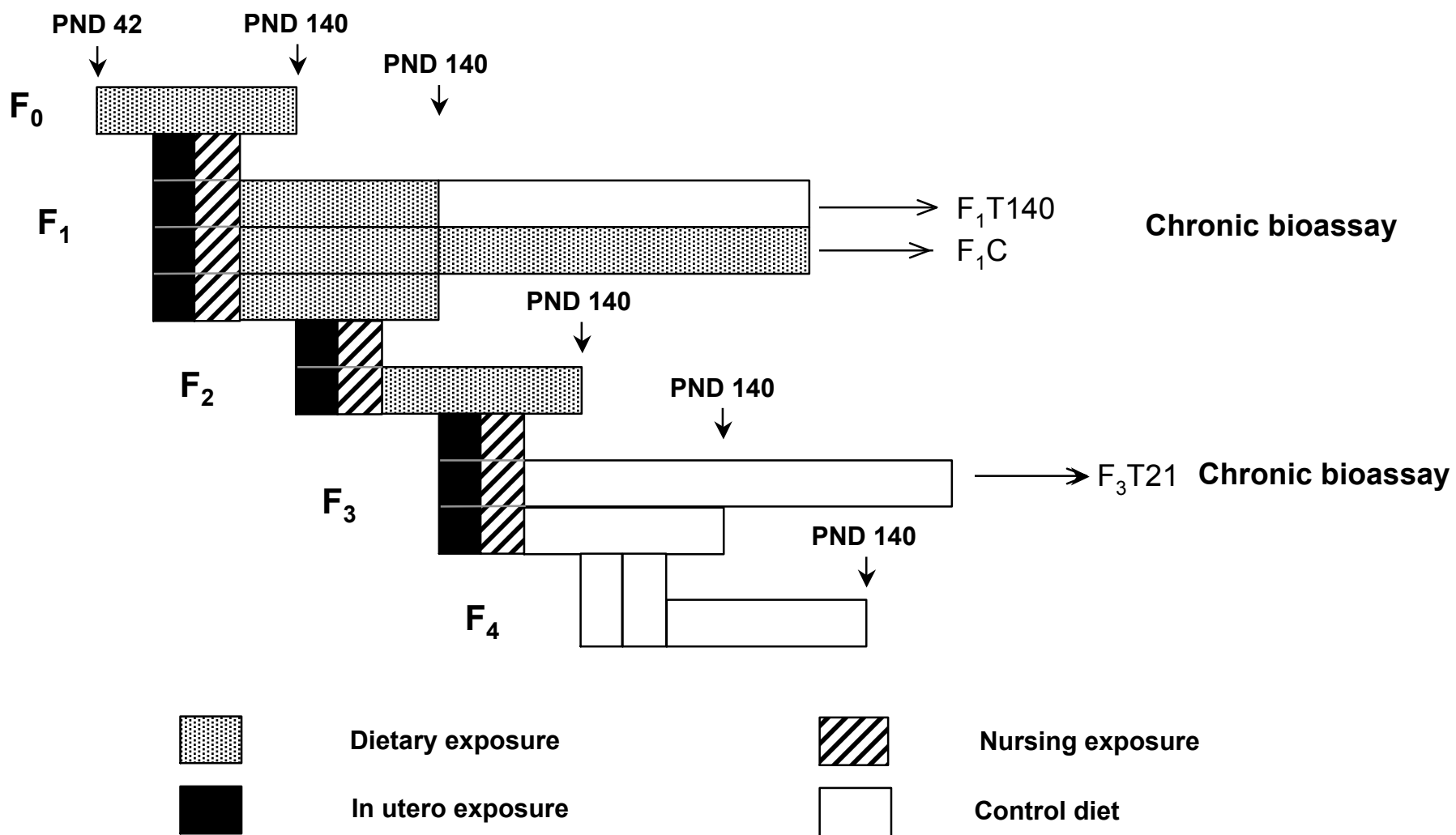


Chronic Study Design

- Dosing (chronic phase)
 - F_1
 - Window 1: Continuous dosing from conception to 2 yrs. (F_1C)
 - Window 2: Dosing from conception to 20 weeks, then control diet to 2 yrs. (F_1T140)
 - F_3
 - Dosing from conception to PND 21, then control diet to 2 yrs. (F_3T21)
- 50 animals per sex per dose group

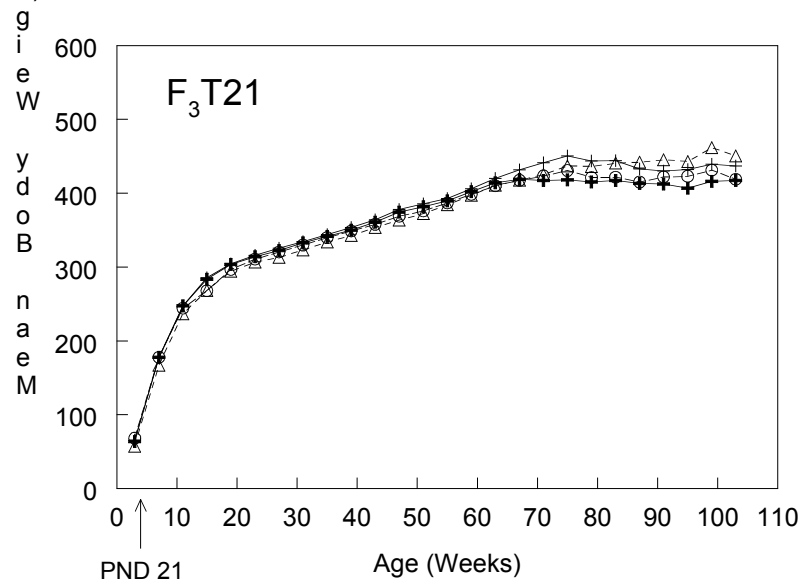
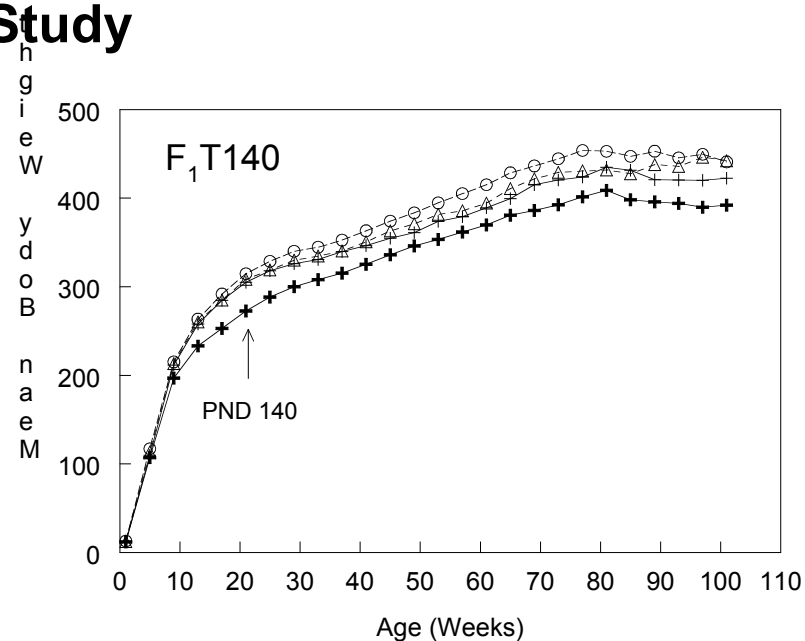
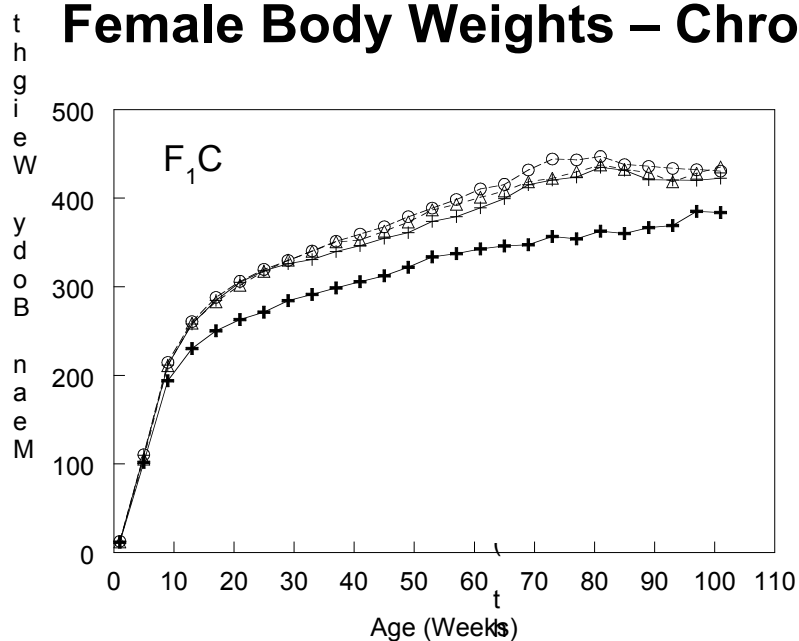


Multigeneration Dosing Scheme



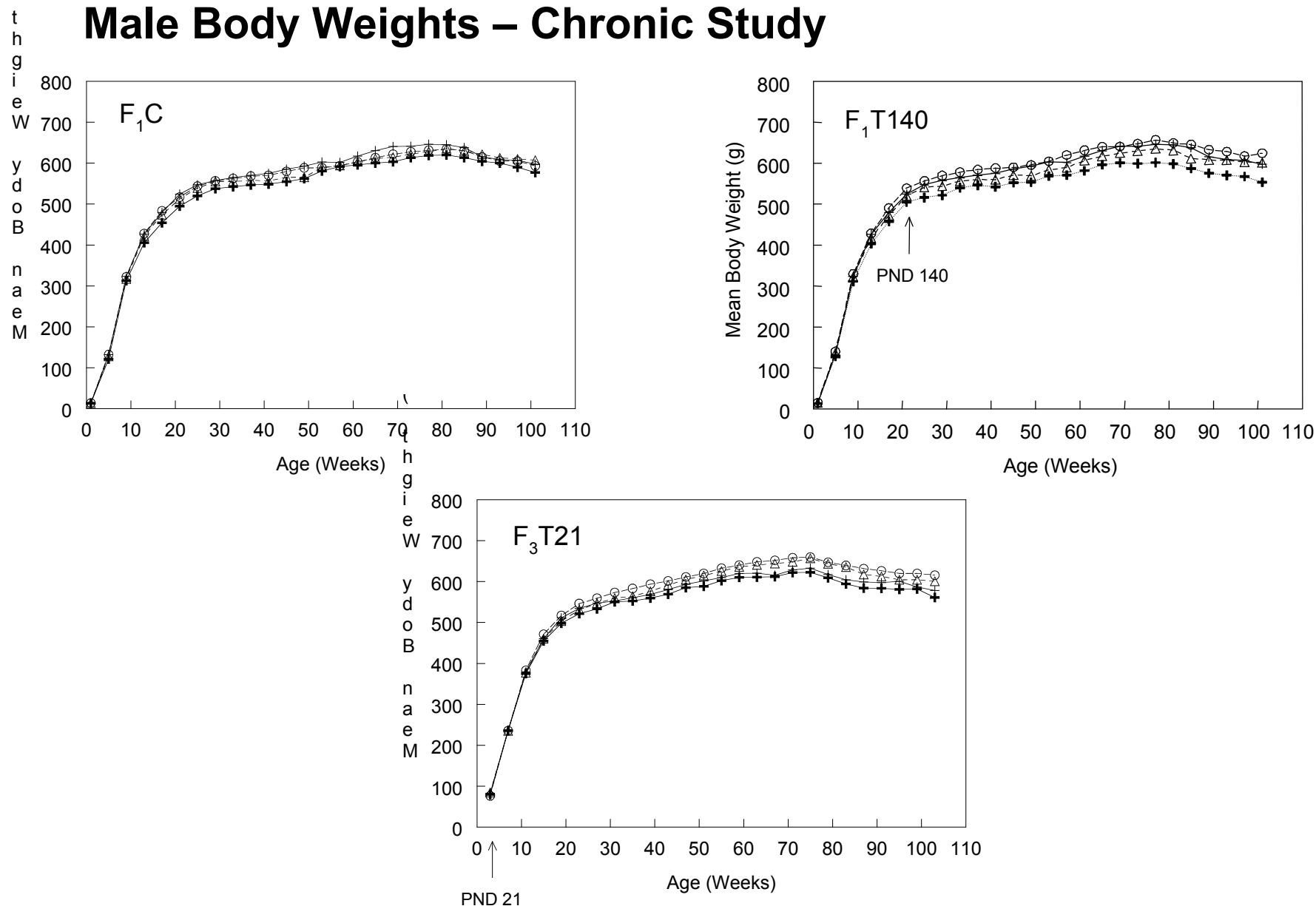


Female Body Weights – Chronic Study



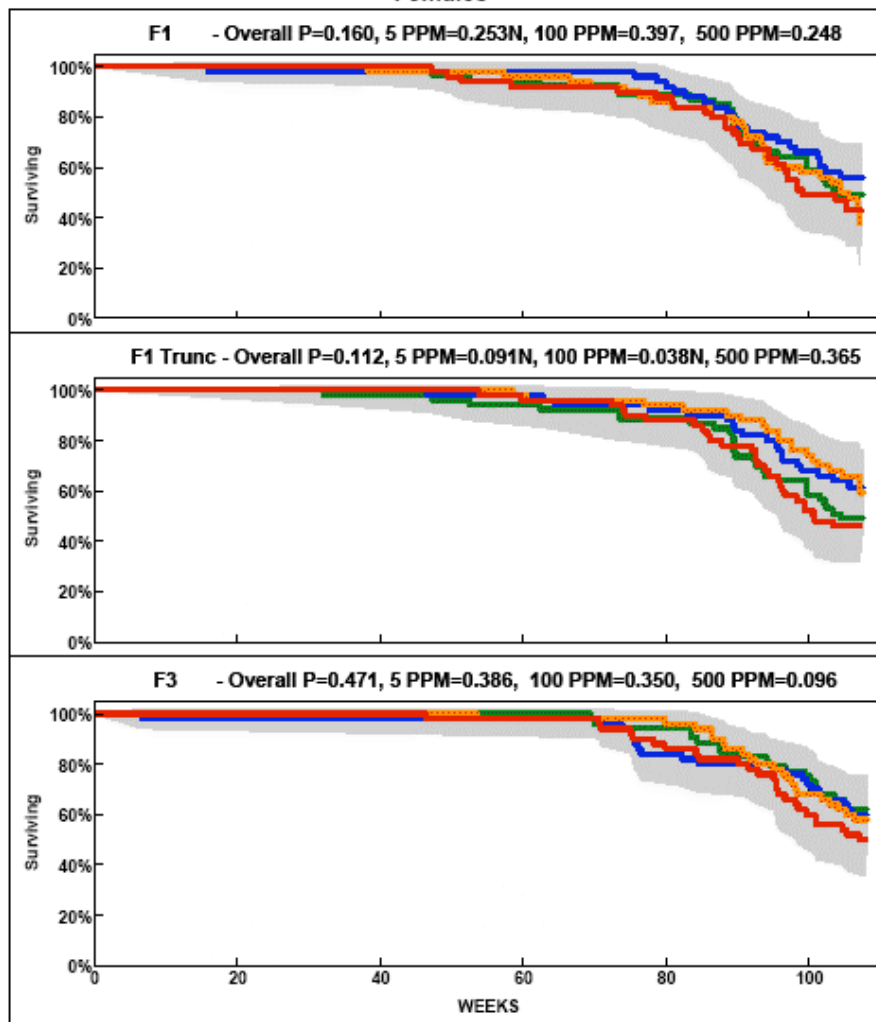


Male Body Weights – Chronic Study





Genistein Chronic Survival
Females

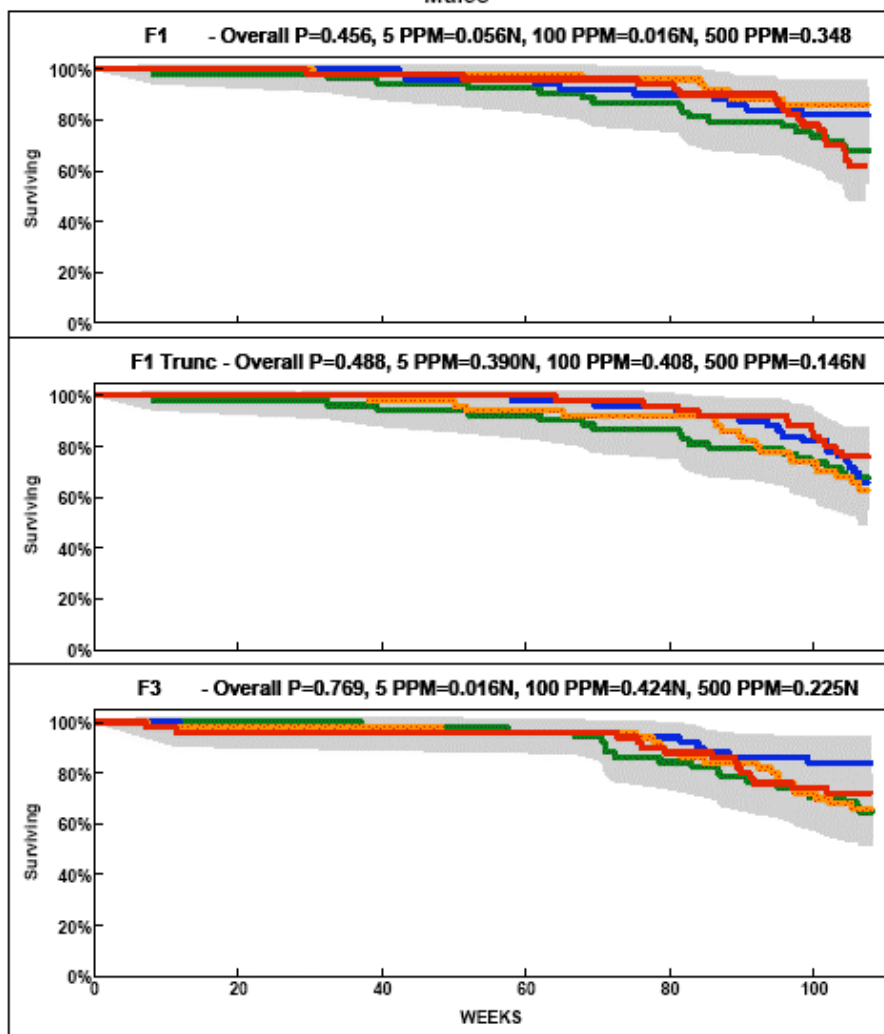


DOSE:

- Control
- 5 PPM
- 100 PPM
- 500 PPM



Genistein Chronic Survival
Males



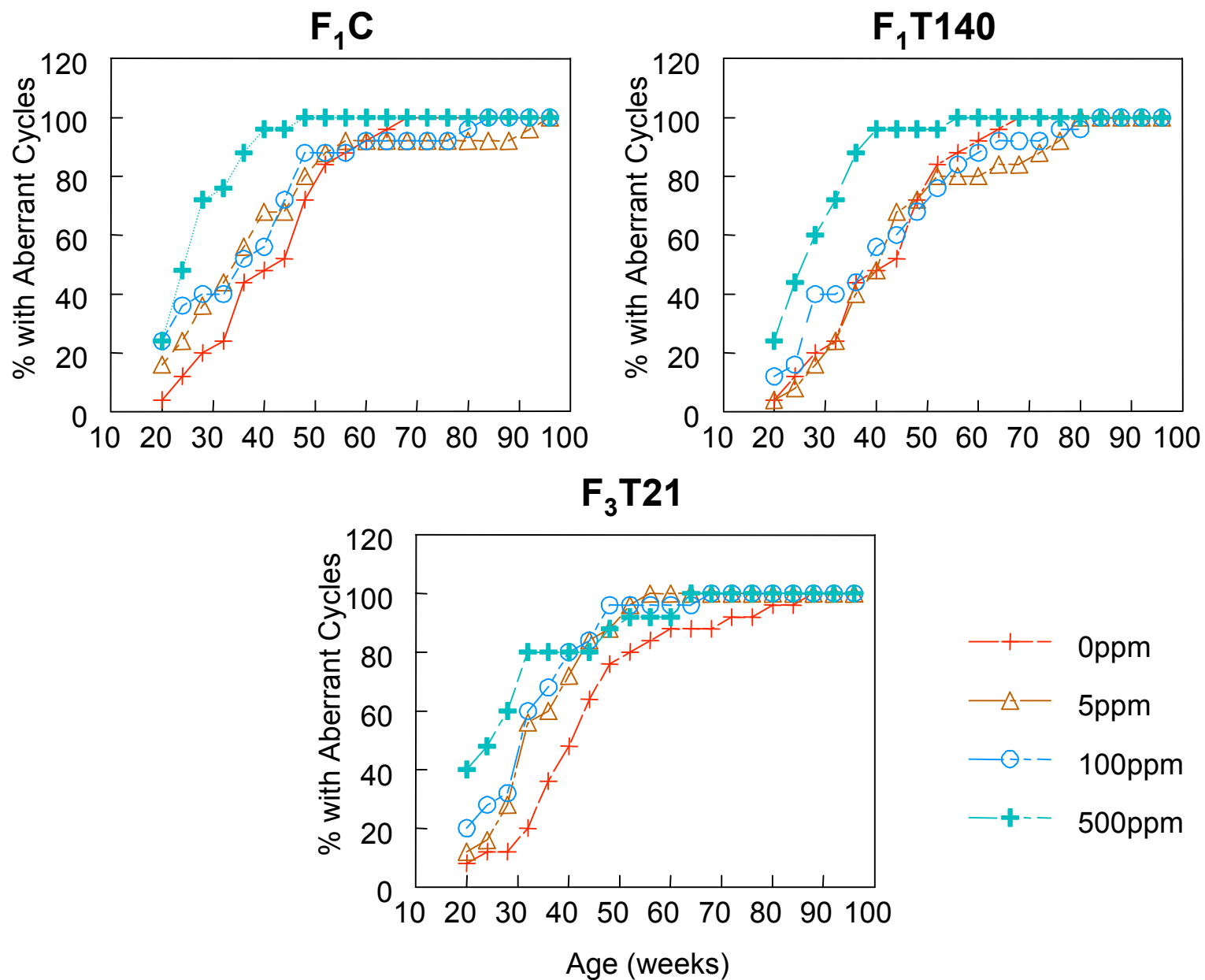
DOSE:

- Control
- 5 PPM
- 100 PPM
- 500 PPM



Vaginal Cytology -Chronic Phase

- Starting at 5 months, lavage a subset (25) of females from each dose group for 5 consecutive days once a month
- Normal cycle is 4-5 days
- Animals not showing cyclicity for 2 months in a row are considered to have aberrant cycles and are not sampled again
- Slides are staged to determine cycle stage; majority of animals in all dose groups were removed in estrus (68 – 96%)



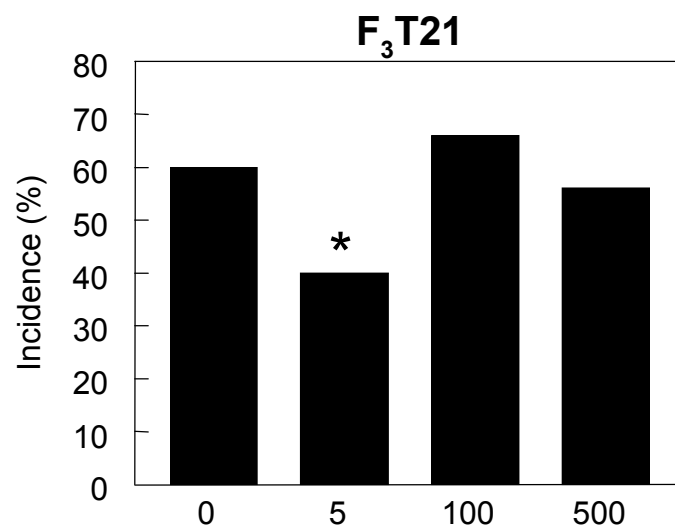
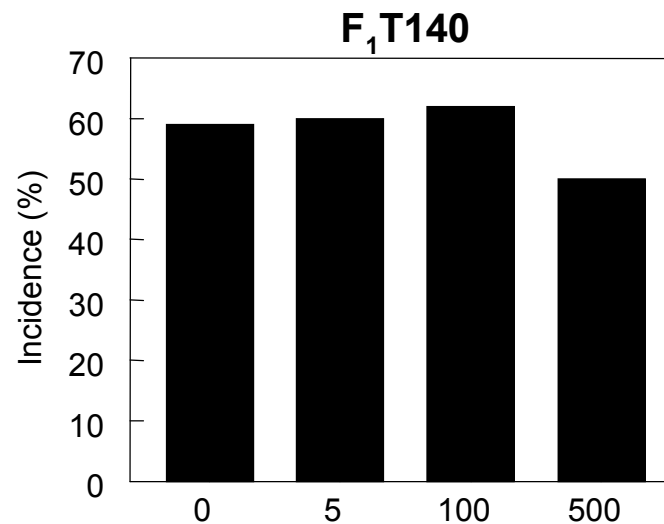
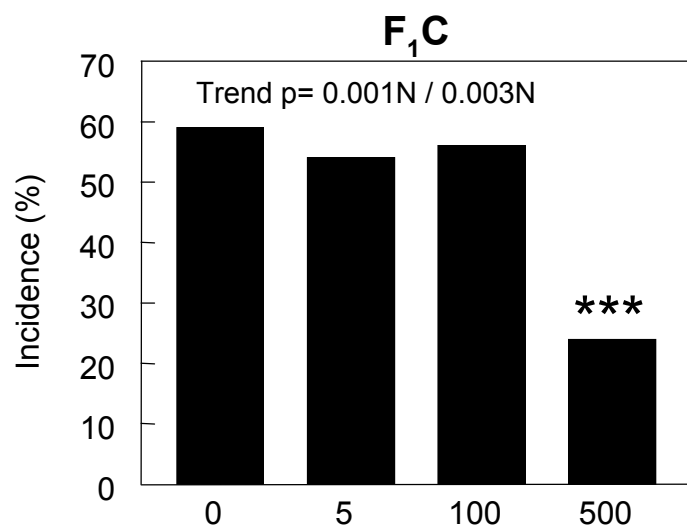


Male Mammary Gland, Alveolar Hyperplasia

Treatment Arm	Affected Animals/Examined Animals (Mean Severity)			
	0 ppm	5 ppm	100 ppm	500 ppm
F₁C*	3/41 (1.7)	2/43 (1.5)	6/40 (1.7)	8/42 (1.4)
F₁T140*	3/41 (1.7)	1/42 (1.5)	1/34 (2.0)	9/45 (1.4)
F₃T21	4/39 (1.5)	5/43 (1.2)	6/41 (1.3)	6/41 (2.0)

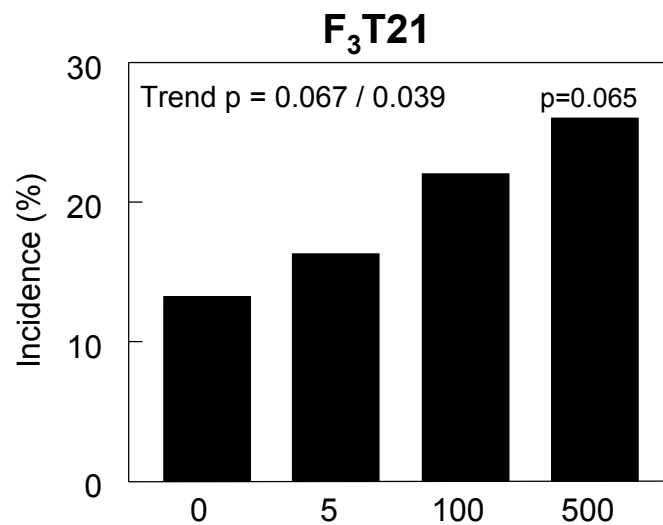
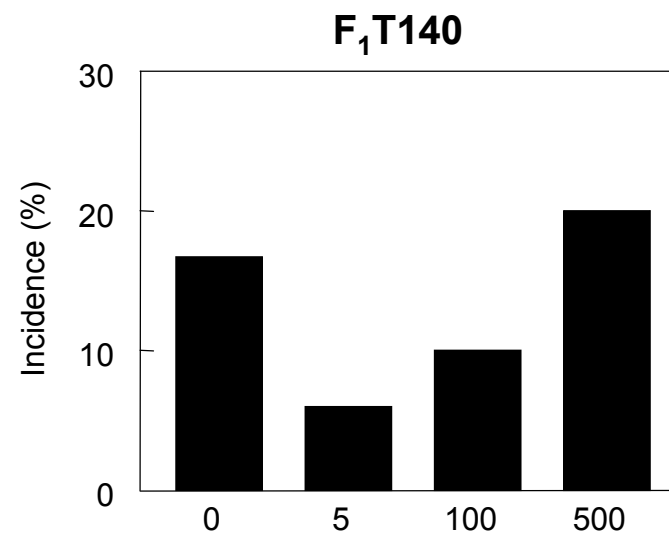
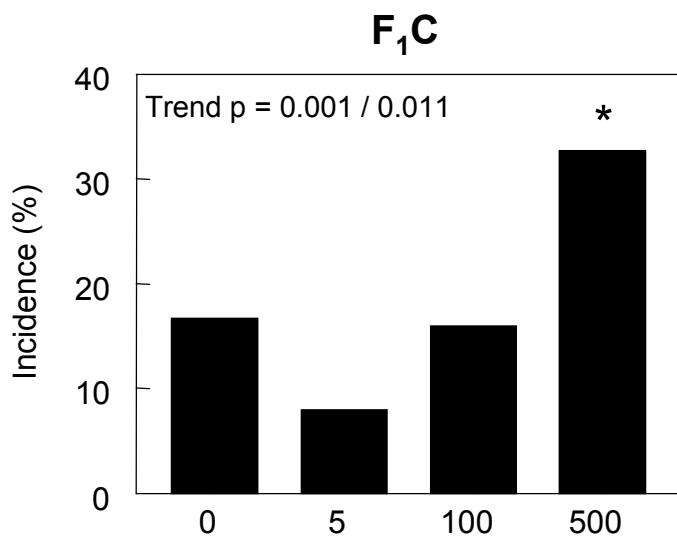


Female Mammary Fibroadenoma



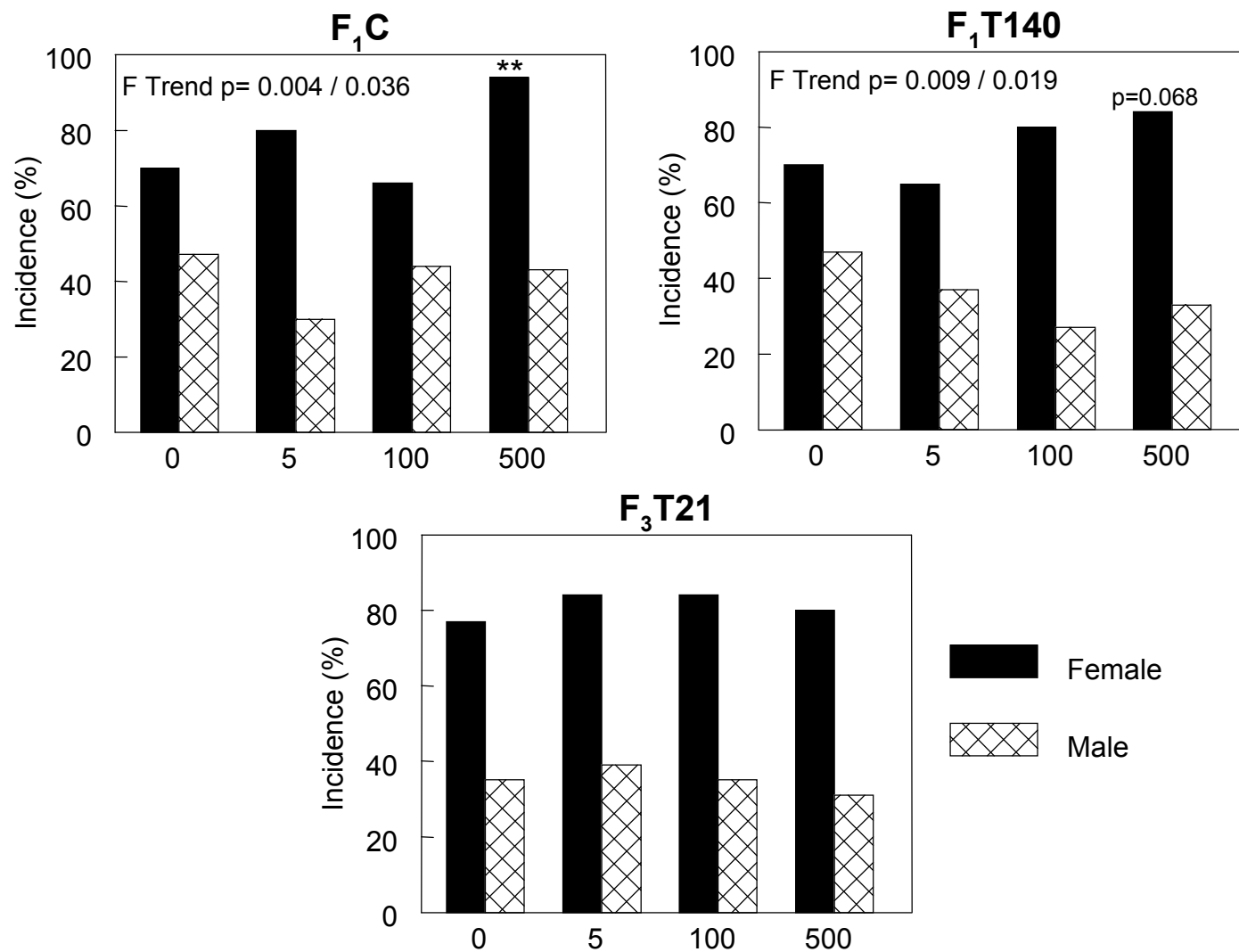


Female Mammary Adenoma/Adenocarcinoma





Pituitary Adenoma



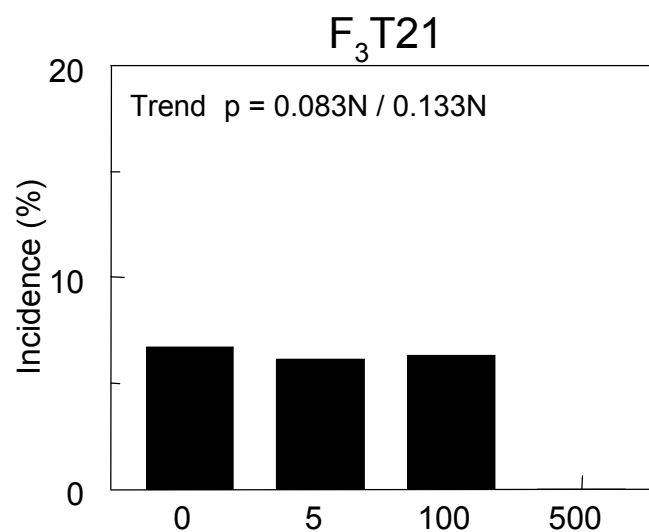
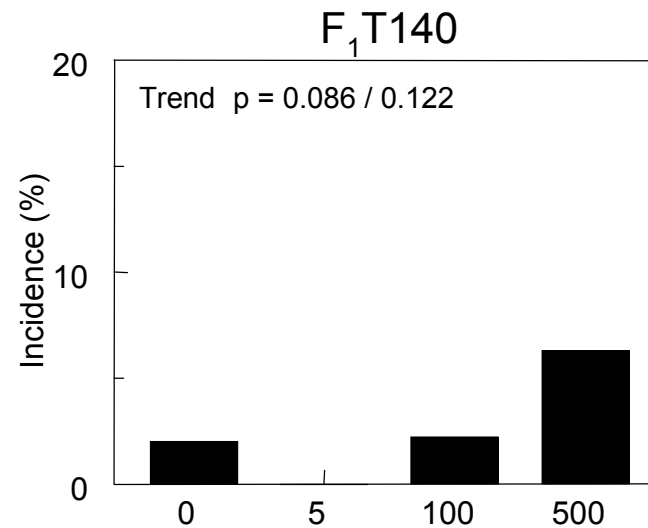
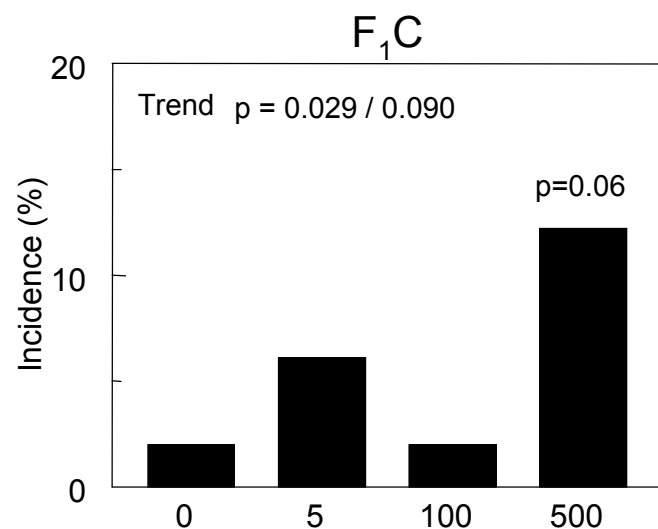


Other neoplastic lesions showing statistically significant trends or dose group vs. control

- Males
 - Pancreatic islet, adenoma or carcinoma (TR 545, Table 8)
 - Preputial gland, squamous cell carcinoma (TR 545, Table 9)
 - Adrenal medulla, pheochromocytoma (TR 545, Table 10)
 - Nose, squamous cell carcinoma (TR 545, Table 11)
- Were not listed in draft report in summary table
 - Based on comparison of two control groups in the present study and limited available historical control data with the NCTR SD rat
 - Studies of Duffy *et al.* using NIH-31 and AIN-93M diets
 - Study of ethinyl estradiol using 5K96 in a protocol identical to the present study (report in preparation)
- Conclusions on pancreatic islet lesions have come under discussion during review of draft report



Male Pancreatic Islet Adenoma/Adenocarcinoma





Conclusions (1): Chronic Study (TR 545)

- Sites affected were common sites for neoplasms in the Sprague-Dawley rat
 - Estrogen sensitive sites
 - Acceleration of time of onset of aberrant cycling
- Significant reduction of mammary fibroadenomas observed in females continuously dosed (F₁C) with 500 ppm genistein
- Other than increased male mammary gland hyperplasia in F₁C and F₁T140 arms, no treatment-related non-neoplastic effects noted



Conclusions (2): Chronic Study (TR 545)

- Males :
 - **No evidence** for neoplastic effects in any of the 3 exposure windows
- Females:
 - Continuous dosing (F₁C): **Some evidence** for neoplastic effects based on significant trends for mammary adenoma/adenocarcinoma, pituitary adenoma, and increased incidence relative to controls for both neoplasms in the 500 ppm dose group
 - Dosing truncated at PND 140 (F₁T140): **Equivocal evidence** for neoplastic effect based on significant trend for pituitary adenoma
 - Dosing truncated at PND 21 (F₃T21): **Equivocal evidence** for neoplastic effect based on significant trend for mammary adenoma/adenocarcinoma